

CASE REPORT



## Oh wait ... It isn't MUDPILES! Acute toxic encephalopathy with an interesting anion gap metabolic acidosis resulting in prolonged invasive mechanical ventilation

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### ABSTRACT

A 70-year-old white female patient with past medical history of migraine, fibromyalgia, diverticulitis, and hypothyroidism presented to the emergency department accompanied by her husband for one day of altered mentation, nausea and vomiting. Laboratory testing showed oligo-anuric acute kidney injury with a severely high anion gap metabolic acidosis. Urine drug screen was negative. Brain imaging and lumbar puncture were negative for acute findings. We report this unique case by going through the differential for anion gap metabolic acidosis secondary to Celecoxib as well as a unique drug–drug interaction between Celecoxib and Gabapentin.

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### KEYWORDS

Celecoxib overdose; NSAID; altered mental status; acute respiratory failure; prolonged mechanical ventilation; gabapentin

## 1. Introduction

Metabolic acidosis is defined as a pathologic process that, when unopposed, increases the concentration of hydrogen ions in the body and reduces the  $\text{HCO}_3^-$  concentration. Acidemia (as opposed to acidosis) is defined as a low arterial pH ( $<7.35$ ), which can result from metabolic acidosis, respiratory acidosis, or both. Not all patients with metabolic acidosis have a low arterial pH; the pH and hydrogen ion concentration also depend upon the coexistence of other acid-base disorders. Thus, the pH in a patient with metabolic acidosis may be low, high, or normal.

Metabolic acidosis can be produced by three major mechanisms including, increased acid generation, loss of bicarbonate and diminished renal acid excretion. Evaluation usually includes, serum or plasma electrolytes, calculation of the anion gap, and a detailed history and physical examination to determine the cause of the metabolic acidosis and guide the therapy. However, in complicated patients, a definitive evaluation of metabolic acidosis usually requires measurements of the arterial pH and  $\text{pCO}_2$  to determine if the respiratory compensation is appropriate or not. Also, assessment of the serum anion gap helps identify the etiology of the acidosis.

## 2. Case presentation

A 70-year-old white female patient with a past medical history of migraine, fibromyalgia, hypertension, diverticulitis, and hypothyroidism presented to the

emergency department accompanied by her husband for one day of altered mental status, nausea and vomiting. Her home medications included furosemide 40 mg once daily, Gabapentin 300 mg three times a day, Hydrocodone-Acetaminophen 7.5/325 mg twice daily as needed, Celecoxib 200 mg twice daily and levothyroxine sodium 125 mcg daily. On physical examination, the patient was alert but did not follow commands, moves all her extremities to painful noxious stimuli only. Her vitals were blood pressure of 153/74 mmHg, heart rate of 86 beats per minute, respiratory rate of 20 saturating 94% on 3 L nasal cannula and a temperature of 98 F. Head CT scan showed no acute findings for stroke or intracranial hemorrhage. Significant laboratories included anion gap 25 meq/l (7–16), lactic acid of 2.6 mmol/l (0.7–2.0), an arterial blood gas with a pH 7.00 nmol/L (7.35–7.45)  $\text{pCO}_2$  8 mmHg (35–45)  $\text{pO}_2$  115 mmHg (80–100)  $\text{HCO}_3^- < 3.0$  mmol/L (22–26). WBC 9.3 K/ul (4.5–11.0), TSH  $< 0.02$  uIU/ml (0.465–4.68), creatinine 1.3 mg/dl (0.7–1.2), BUN 20 (7–17) m/dl. She was emergently intubated for airway protection. Urinalysis and drug screen were negative for acute findings including ethylene glycol. The patient became oliguric with creatinine of 4.6 mg/dl. Repeat brain imaging with CT and MRI showed no evidence for acute stroke or intracranial hemorrhage. Head and neck MRA did not have evidence of stenosis. There were no acute processes on CT abdomen and pelvis and chest x-ray. Patient was alert but unresponsive on ventilator despite being off sedation. Significant findings on lumbar puncture were a WBC

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of 10.0 cells/ul (0–5), a CSF total protein 223.0 mg/dl (12–60) a CSF glucose 61 md/dl (40–70) and a negative gram stain. CSF cultures were negative. Electroencephalogram with no significant findings for any possible seizures. Her creatinine peaked at 7.1 mg/dl on the third day of her hospital stay with BUN 96 mg/dl. Patient became anuric. Dialysis was started. By her second session, her creatinine was noted to trend down. After five daily dialysis sessions the patient's consciousness and responsiveness returned, and she was extubated. Patient was discharged to inpatient rehab. Her husband later found her Celecoxib bottle to be empty after refilling it for one month's supply just prior to her presentation. We were unsure of how many pills the patient had ingested but her diagnosis was reached by exclusion.

### 3. Discussion

The cyclooxygenase (COX)-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs; coxib's) share several potential risks for adverse events with other NSAIDs, including increased risk of cardiovascular adverse events, renal compromise, and others, despite their potential for reducing the likelihood of gastroduodenal ulcers.

NSAIDs, including the COX-2 selective agents, can induce several different forms of kidney injury. COX-2 selective NSAIDs as well as nonselective NSAIDs may cause acute kidney injury (AKI) by the attenuation of renal vasodilation in patients in whom the secretion of vasodilator prostaglandins is increased to counteract the effect of increased renal vasoconstrictors such as angiotensin II. Risk factors for NSAID-induced AKI include chronic kidney disease (CKD); volume depletion from aggressive diuresis, vomiting or diarrhea, or effective arterial volume depletion due to heart failure, nephrotic syndrome, or cirrhosis; and severe hypercalcemia. Medications including diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), Gabapentin and calcineurin inhibitors (CNIs) also can increase the risk of NSAID-induced AKI. Higher doses of NSAIDs are associated with a greater risk of AKI.

There is relatively little data directly comparing the renal risk of COX-2 selective with nonselective NSAIDs. However, there is evidence from the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial that celecoxib may be associated with fewer clinically significant renal events than ibuprofen [1,2].

Anion gap metabolic acidosis (AGMA) occurs because of excess organic anions. The differential is wide including various causes such as alcohol, medications, ketosis, uremia, both L and D lactic acidosis, and salicylate toxicity [3].

In this patient, due to the anion gap as well as her symptoms, the differential included intoxication, infection, uremia, ketosis, and medication induced AGMA. Her blood and urine drug screen were negative for ethanol and ethylene glycol. Urinalysis was negative for any crystals or pyuria. Chest X-ray had no acute cardiopulmonary process. Lactic acid was initially elevated on admission but trended down quickly. The AGMA, however, was persistent. Urine and serum ketones were negative, ruling out ketosis. Aspirin is another potential cause of AGMA that results in an additional respiratory alkalosis. This patient did have a respiratory alkalosis; however, her urine was negative for salicylates. While her BUN did eventually increase to 96 m/dl from 20 m/dl, making uremia lower on the differential.

Medication induced AGMA in this case Celecoxib was the most likely etiology. The anion gap is likely secondary to accumulation of metabolites which are acidic (specifically carboxylic acid). Our patient had taken a significant amount of Celecoxib, resulting in a large anion gap initially as shown in (Table 1) with an elevated anion gap on admission. As Celecoxib underwent hepatic metabolism via CYP2C9, the anion gap decreased [4,5].

In addition, Celecoxib has been shown to have a dose dependent renal toxicity as discussed above. This is likely mediated by inhibition of prostaglandin synthesis, resulting in vasoconstriction of the afferent arterioles. This vasoconstriction results in decreased glomerular filtration rate, oliguria, and potentially anuria as in this case. Celecoxib induced renal injury should respond to fluids and supportive management, this patient unfortunately developed anuria, requiring dialysis [6].

Finally, her prolonged altered mental status was presumed to be secondary to Gabapentin. In anuric patients, Gabapentin can remain in the system for up to 132 hours. With dialysis, however, this decreases to 3.8 hours [7]. Gabapentin toxicity resulted in a prolonged period of time on the ventilator due to altered mentation. After the patient had her second round of dialysis her mental status improved significantly, as Gabapentin was cleared. This case represents an

**Table 1.** Table showing significant laboratory values during admission, intubation, dialysis day one and extubation day.

Laboratory value/ Day	Admission Day	Intubation Day	Dialysis Day 1	Extubation Day
pH (nmol/L)	7.00	7.09	N/A	7.44
Bicarbonate (mmol/L)	7	9	22	26
Anion gap (MEQ/L)	25	30	14	13
BUN (mg/dl)	20	30	95	46
Creatinine (mg/dl)	0.9	3.3	7.1	4.6
Lactic Acid (mmol/l)	2.6	2.2	N/A	N/A

interesting instance in which a patient developed anuric renal failure due to Celecoxib toxicity resulting in decreased clearance of Gabapentin, resulting in prolonged mechanical ventilation.

#### 4. Conclusion

In conclusion, here we present a unique case in which a patient overdosed on celecoxib resulting in an AGMA and acute renal failure with presumed Gabapentin toxicity. Treatment with dialysis was eventually needed to clear the Gabapentin, allowing for improvement in mental status in addition to addressing the patient's anuria.

#### Disclosure statement

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#### Informed consent

Verbal Consent was obtained directly from the patient to publish this manuscript.

#### Ethics approval

Our institution does not require an ethics approval for reporting individual cases.

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